Subcortical vascular dementia: Integrating neuropsychological and neuroradiologic data

C. C. Price, A. L. Jefferson, J. G. Merino, K. M. Heilman and D. J. Libon

Neurology 2005;65;376-382; originally published online Jul 6, 2005;
DOI: 10.1212/01.WNL.0000168877.06011.15

Subcortical vascular dementia

Integrating neuropsychological and neuroradiologic data

C.C. Price, PhD; A.L. Jefferson, PhD; J.G. Merino, MD; K.M. Heilman, MD; and D.J. Libon, PhD

Abstract—*Background:* Research criteria for subcortical vascular dementia are based on radiologic evidence of vascular pathology and greater impairment on tests of executive control than memory. The relationship(s) between neuroradiological evidence of subcortical vascular disease and neuropsychological impairments has not been specified. *Objective:* To define these research criteria, the authors rated the severity of MRI white matter abnormalities (WMAs) and neuropsychological data from patients with dementia. *Methods:* Sixty-nine outpatients who met the criteria for dementia were studied with neuropsychological tests that assessed executive (mental) control, declarative memory, visuoconstruction (clock drawing), and language (semantic category fluency). MRI-WMAs were rated using a leukoaraiosis (LA) scale (range 0 to 40). *Results:* First, regression analyses demonstrated that neuropsychological measures accounted for 60.7% of the variance in WMA severity (47.3% of this variance attributable to executive/visuoconstructive test performance, 13.4% attributable to memory/language test performance). Second, patients were grouped according to the severity of WMAs (i.e., low, moderate, and severe white matter groups). Only patients with mild WMA (mean LA = 3.61 ± 2.63, approximately 2.4 to 15.6% of the subcortical white matter) presented with greater impairment on memory/language tests vs executive control/visuoconstructive tests, a neuropsychological profile typically associated with Alzheimer disease. Patients with moderate WMA (mean LA = 12.76 ± 2.49, approximately 25.6 to 38.1% of the subcortical white matter) presented with equal impairment on executive/visuoconstructional vs memory/language tests. Patients with severe WMA (mean LA = 21.76 ± 2.97, approximately 46.9 to 62.4% of the subcortical white matter) displayed a profile of *greater* executive/visuoconstructional impairment relative to memory/language disabilities. *Conclusion:* A profile of *equal* impairment on tests of executive control and memory along with radiologic evidence involving about one-fourth of the cerebral white matter as measured by the Leukoaraiosis Scale may be sufficient for a diagnosis of subcortical vascular dementia.

NEUROLOGY 2005;65:376–382

Various diagnostic criteria for vascular dementia (VaD) have been proposed.[1-4] Disparate degrees of specificity have been shown when these diagnostic criteria are compared,[5-10] suggesting that VaD has a heterogeneous presentation. Modifications have been proposed to existing diagnostic criteria for a single subtype of VaD: subcortical VaD.[10,11] These modified diagnostic criteria require radiologic evidence of subcortical cerebrovascular disease and a neuropsychological profile demonstrating greater impairment on executive functions relative to the delayed recognition memory. Although this proposal provides some guidelines regarding the amount of white matter abnormalities (WMAs) necessary for a diagnosis of subcortical VaD, the exact relationship(s) between neuroradiologic evidence of subcortical vascular disease and performance on tests of executive control and memory is not specified. This study was designed to specify these relationships.

We sought to define the relationships between the extent of WMAs seen on MRI and performance on neuropsychological tests assessing executive control and visuoconstructional abilities vs language and memory abilities. Separate indexes measuring performance on tests of executive control/visuoconstruction vs language/memory functions were constructed. Prior research has shown dissociations such that dementia patients with significant WMAs obtain lower scores on executive/visuoconstruction tests, whereas dementia patients with little white matter disease produce lower scores on language/memory tests.[12,13]

Implicit in this research is the concept of a WMA threshold, that is, how much MRI WMA is necessary for patients to demonstrate greater impairment on executive control/visuoconstructional abilities relative to language/memory abilities. By grouping patients on the basis of MRI WMAs, between- and within-group analyses can be conducted to assess for unique patterns of neuropsychological impairment. Therefore, our prediction is that there will be a dou-

This article was previously published in electronic format as an Expedited E-Pub on July 6, 2005, at www.neurology.org.

From the Departments of Clinical and Health Psychology and Anesthesiology (Dr. Price) and Neurology (Drs. Merino and Heilman), University of Florida, and Veteran Affairs Medical Center (Dr. Heilman), Gainesville, FL; Department of Psychiatry and Human Behavior (Dr. Jefferson), Brown Medical School, Providence, RI; and Center for Aging (Dr. Libon), School of Osteopathic Medicine, University of Medicine and Dentistry of New Jersey, Stratford, NJ.

Disclosure: The authors report no conflicts of interest.

Presented in part at the First Congress for the Study of Vascular Cognitive and Behavioral Disorders, Goteberg, Sweden, 2003.

Received February 16, 2004. Accepted in final form April 21, 2005.

Address correspondence and reprint requests to Dr. D.J. Libon, Center for Aging, School of Osteopathic Medicine, University of Medicine and Dentistry of New Jersey, 42 E. Laurel Rd., Suite 1800, Stratford, NJ 08084; e-mail: libondj@UMDNJ.edu

Table 1 *Mean (SD) of white matter abnormality (WMA) score and demographics for patient group classifications*

Group	WMA score*	Age, y	Education, y	MMSE	GDS
Mild WMA	3.61 (2.63)	77.81 (5.58)	12.48 (2.46)	22.26 (3.39)	5.97 (3.62)
Moderate WMA	12.76 (2.49)	78.67 (4.97)	11.57 (2.42)	22.71 (3.47)	7.76 (3.58)
Severe WMA	21.76 (2.97)	77.41 (6.60)	11.29 (3.29)	20.65 (4.68)	5.71 (2.39)
All patients	10.87 (7.86)	77.97 (5.61)	11.91 (2.69)	22.00 (3.79)	6.45 (3.42)

* WMA score = Junque Leukoaraiosis Scale score (score range = 0–40).

MMSE = Mini-Mental State Examination (score range = 0–30); GDS = Geriatric Depression Scale (score range = 0–30).

ble dissociation such that patients in the low MRI WMA group will present with greater impairment on tests of language/memory than executive control/visuoconstruction ability. Patients in the high MRI WMA group are expected to produce the opposite profile. These findings might help define the threshold of WMA burden at which point executive control/visuoconstruction impairments exceed language/memory deficits and thus aid in the development of research criteria for subcortical VaD.[10]

Methods. *Patients.* We studied 128 consecutive patients drawn from the Crozer–Chester Medical Center Alexander Silberman Geriatric Assessment Program, a community-based outpatient memory assessment program. Most dementia patients were self-referred or referred by a primary care physician. Medical history was gathered from a knowledgeable family member. Brain MRI scan and diagnostic laboratory studies were obtained to evaluate for reversible causes of dementia. Exclusion criteria included MRI evidence of cortical infarctions, history of head injury, substance abuse, major psychiatric disorders, epilepsy, vitamin B_{12}, folate, or thyroid deficiency, or chronic medical conditions that could influence cognition. All patients gave informed consent, and an institutional review committee approved the study.

Of the 128 patients, 17 patients were excluded because of a medical illness that could influence cognition. Forty-two patients were excluded owing to missing data. Diagnoses were determined by consensus between a neurologist, neuropsychologist, psychiatrist, geriatrician, and social worker. The final sample consisted of 69 outpatients with dementia, 34 who met criteria for diagnosis of Alzheimer disease[14] (AD) and 35 who met criteria for the diagnosis of probable/possible ischemic VaD[3] (table 1). No patient reported sudden onset or step-wise decline of cognitive function.

MRI protocol. A 1.5 T Siemens magnetic scanner (Erlangen, Germany) was used. Both T1-weighted (repetition time [TR] 500 milliseconds, echo time [TE] 15 milliseconds) and T2-weighted (TR 4,000 milliseconds, TE 90 milliseconds) studies were obtained. The severity of WMAs was quantified using a semiquantitative 40-point scale: the Junque Leukoariasiosis Scale (LA Scale).[15] This scale divides each hemisphere into five areas: frontal centrum semiovale, parietal centrum semiovale, white matter around the frontal horns, white matter around the body of the lateral ventricles, and white matter around the atrium and the occipital horns. The severity of WMAs in each area was graded from 0 (no visible WMA) to 4 (severe WMA), and then all area scores were summed (WMA score range = 0 to 40). WMA scores were calculated by two board-certified neuroradiologists who were blind to all clinical information (interrater reliability, $r = 0.98$, $p < 0.001$).[12] The validity of the LA Scale is based on prior studies from different laboratories showing high LA scores correlate with poorer performance on tests of executive control and information-processing speed.[12,13,15,16]

Patient groups. Patients clinically diagnosed with either AD or VaD were regrouped according to the severity of WMAs using the 40-point LA Scale.[15] Currently, there is no literature that offers a totally validated operational definition of the significance of MRI WMAs. A frequency distribution of our 69 patients indicated that the LA Scale score ranged from 0 to 28. To assign patients into the mild, moderate, or severe MRI WMA groups, we divided the scale into three relative portions. We created groups where on average approximately 10% (mild, LA = 0 to 8; n = 31), 32% (moderate, LA = 9 to 17; n = 21), and 54% (severe, LA = 18 to 28; n = 17) of the total white matter as seen on MRI was involved.

Neuropsychological assessment. The neuropsychological protocol described below was selected because the validity of these measures has been well established.

Executive control was assessed with the Boston Revision of the Wechsler Memory Scale–Mental Control Subtest[17] (WMS-MC). In addition to the three tasks that comprise the standard WMS-MC Subtest (i.e., counting from 20 to 1, reciting the alphabet, and adding serial 3's),[18] the WMS-MC includes four additional tasks: reciting the months of the year forward and backward, identifying letters that rhyme with the word "key," and naming block-printed letters that contain curved lines (e.g., "b, c, d," etc.). Patients were allowed to work as long as necessary provided that they worked meaningfully. The dependent variable was an accuracy index (AcI) derived from the three nonautomatized tasks (i.e., months backward, alphabet rhyming, and alphabet visualization). The AcIs for each nonautomatized task were based on the following algorithm: AcI = (1 - [false positives + misses/possible correct]) * 100. This algorithm yields a percentage score ranging from 0 to 100% (100% correct results in the correct identification of all targets with no misses or false-positive responses). A composite AcI score was calculated by averaging the AcI values from these subtests. Prior research has shown that performance on these tests is very sensitive to the volume of white matter disease in patients with mild dementia.[17] Similar tasks have been shown to activate the prefrontal cortex.[19]

Visuoconstruction ability was assessed by asking patients to draw a clock face to command and to copy with hands set for "ten after eleven."[20] Following published procedures,[21] 10 errors related to graphomotor impairment, hand/number placement, and executive control were scored as either 1 (present) or 0 (absent) for both command and copy conditions (range 0 to 20 errors). Previous research has shown that total errors summed across the command and copy conditions are highly correlated with performance on tests of executive control and visuospatial ability.[21-23] Therefore, the dependent variable derived from this test was the total number of errors summed across the command and copy test conditions. This test appears to be diagnostically sensitive test for subcortical VaD.[23,24] Data from our laboratory show a high correlation between total clock-drawing errors and copy of the Rey Complex Figure[24,25] (−0.570 to −0.649, unpublished data).

Language functioning was assessed with the "animal" word list generation task.[26] The total number of animals generated was not used as a dependent variable in this research. Rather, the dependent variable derived from the "animal" fluency task was the total association index ("animal" AI),[26] a special scoring technique believed to measure the semantic organization between successive responses. A high AI score is believed to reflect relatively intact semantic memory stores.[13,26] Recent studies have shown that performance on category fluency tests tends to activate the left temporal lobe.[27,28]

Declarative memory was assessed with the nine-word dementia version of the California Verbal Learning Test (CVLT).[29] Declarative memory may be characterized as ability to encode and retrieve new information.[30] The dependent variable was the delayed recognition discriminability index ($CVLT_{discrim}$) (algorithm = [1 - (false positives + misses)/total possible correct] x 100). A high $CVLT_{discrim}$ is believed to reflect the ability to encode

Table 2 *Neuropsychological data: Mean (SD) of test scores and z scores reported for all patients and by WMA group*

	All patients	Mild WMA	Moderate WMA	Severe WMA
WMS AcI				
Test score	58.60 (23.78)	71.88 (14.90)	58.61 (22.50)	34.34 (19.71)
z score	–3.08 (2.22)	−1.81 (1.40)	−3.12 (2.06)	−5.35 (1.85)
Clock-drawing errors				
Test score	4.66 (2.61)	3.16 (1.46)	5.04 (2.45)	6.94 (2.72)
z score	−1.99 (1.70)	−1.02 (.95)	−2.20 (1.63)	−3.48 (1.77)
"Animal" AI				
Test score	3.09 (0.94)	2.61 (0.92)	3.25 (0.82)	3.75 (0.62)
z score	−0.89 (1.65)	−1.72 (1.62)	−0.60 (1.43)	0.27 (1.09)
CVLT-discrim				
Test score	73.54 (13.73)	65.39 (13.91)	80.19 (10.95)	80.18 (7.40)
z score	−4.57 (2.88)	−6.27 (2.89)	−3.18 (2.34)	−3.11 (1.56)

WMA = white matter abnormality; WMS AcI = Wechsler Memory Scale nonautomatized accuracy index; "Animal" AI = "animal" word list generation association index; CVLT-discrim = California Verbal Learning Test dementia version discriminability index.

new information into long-term memory.[31] Prior research has shown that patients with subcortical pathology perform better on the recognition condition from the CVLT than on the free recall condition.[31,32] This suggests that patients with subcortical pathology are able to encode new information and their memory difficulty is primarily a retrieval deficit.[33]

Statistical analyses. First, we conducted simple correlations and a step-wise regression analysis to assess how neuropsychological performance relates to increasing WMA. Second, a 3 (low, moderate, severe WMA groups) x 2 (executive/visuoconstruction vs memory/language indexes) repeated measures analysis of variance (ANOVA) assessed the dissociation between neuropsychological tests among patients with mild, moderate, and severe WMA. There were no between-group differences among demographic variables, and the mean (SD) WMA scores are shown in table 1. Also, when the VaD group was examined separately, there were no differences on any demographic or neuropsychological variables when patients with lacunes were compared with patients without lacunes.

All neuropsychological data were converted to *z* scores on the basis of an age- and education-matched elderly control group. This procedure is required to conduct the ANOVA described above and to assess the pattern of neuropsychological deficits within each group. The control participants (n = 18) were living in the community and obtained scores on the Mini-Mental State Examination[34] (MMSE) of ≥27 and Geriatric Depression Scale[35] of <10. Using *z*

Table 3 *Stepwise regression analysis: Dependent variable = WMA (as obtained by Junque score), independent variables = neuropsychological tests*

Step	Model	R	R^2	F change	df	Significant F change
1	MMSE	0.139	0.019	1.31	1/67	0.256
2	MMSE					
	Clock errors	0.591	0.350	33.56	1/66	0.001
3	MMSE					
	Clock errors					
	WMS-MC	0.688	0.473	15.14	1/65	0.001
4	MMSE					
	Clock errors					
	WMS-MC					
	CVLT-discrim	0.745	0.555	11.91	1/64	0.001
5	MMSE					
	Clock errors					
	WMS-MC					
	CVLT-discrim					
	"Animal" AI	0.779	0.607	8.21	1/63	0.006

WMA = white matter abnormality; MMSE = Mini-Mental State Examination; WMS-MC = Wechsler Memory Scale–Mental Control Subtest; CVLT-discrim = California Verbal Learning Test dementia version discriminability index; "Animal" AI = "animal" word list generation association index.

Table 4 *Between-group performance on executive/visuoconstructive vs memory/language indexes: z score mean (SD)*

Parameter	Mild WMA, n = 31	Moderate WMA, n = 21	Severe WMA, n = 17	Significance	*p*
Executive/visuoconstruction					
z score mean (SD)	−1.42 (0.77)	−2.66 (1.57)	−4.41 (1.48)	Mild < moderate	<0.001
				Mild < severe	<0.001
				Moderate < severe	<0.001
Memory/language					
z score mean (SD)	−4.00 (1.68)	−1.88 (1.60)	−1.41 (0.83)	Mild > moderate	<0.001
				Mild > severe	<0.001
				Moderate = severe	NS

WMA = white matter abnormality.

scores, two neuropsychological indexes were created from the four neuropsychological dependent variables. The *z* scores from the WMS-MC AcI and total clock-drawing errors were averaged to create an executive control/visuoconstruction index. The *z* scores from the $CVLT_{discrim}$ index and "animal" AI were averaged to create a memory/language index.

Results. Of the patients diagnosed with VaD, 15 presented with small cerebrovascular accidents involving the basal ganglia (n = 9), thalamus (n = 6), internal capsule (n = 2), and corona radiata (n = 2) (table 2).

Relationship between neuropsychological performances and increasing WMAs. Simple correlations. Pearson product–moment correlations between the WMA scores and neuropsychological tests were conducted. There was little association between the MMSE and the MRI WMA score (r = -0.16, NS). By contrast, all four neuropsychological variables were significantly related to the severity of MRI WMA. Thus, as the WMA score increased, patients obtained lower scores on the WMS-MC AcI (r = -0.56, $p < 0.001$) and made more errors on their clock drawings (r = 0.53, $p < 0.001$). Patients with greater WMAs obtained a higher score on the $CVLT_{discrim}$ ($r = 0.36$, $p < 0.001$) and a higher score on the "animal" fluency AI ($r = 0.43$, $p < 0.001$), demonstrating relative preservation of semantic/lexical stores.

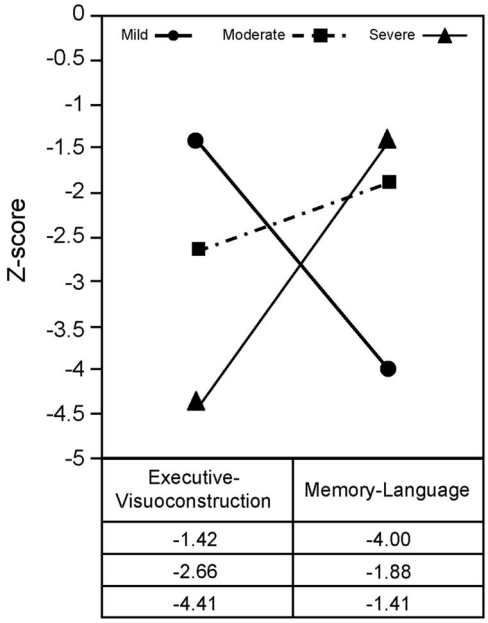

Figure. Mild, moderate, and severe white matter abnormality (WMA) groups and corresponding executive/visuoconstructive and memory/language z scores.

Step-wise regression analysis. The dependent variable was the MRI WMA score, and the independent variables were the MMSE score as well as the four other neuropsychological variables. This analysis was significant ($F[5,63] = 19.43$, $p < 0.001$; $R = 0.779$, $R^2 = 0.607$) (table 3). The MMSE accounted for 5% of the variance regarding the WMA score. All neuropsychological measures accounted for 60.7% of WMA score variance. Both executive control and visuoconstruction ability accounted for approximately 47.3% of the variance in this model. The memory and language measures accounted for an additional 13.4% of the variance. Thus, consistent with our prediction, executive/visuoconstruction ability and memory/language tests explained increasing unique amounts of variance with respect to the LA Scale.

Neuropsychological differences between mild, moderate, and severe WMA groups. Repeated measures ANOVA. A 3 (mild [n = 31], moderate [n = 21], severe [n = 17] WMA groups) x 2 (executive/visuoconstruction vs memory/language indexes) repeated measures ANOVA tested our prediction of an interaction between WMA groups and neuropsychological test performance. This analysis yielded a two-way interaction ($F[2, 66] = 51.75$, $p < 0.001$). There were no significant main effects.

Between-group post-hoc analyses were first conducted with two separate univariate ANOVAs (table 4). Both of these analyses were significant (executive/visuoconstruction: $F[2, 66] = 31.73$, $p < 0.001$; memory/language: $F[2, 66] = 21.14$, $p < 0.001$). Between-group pairwise comparisons were carried out with Tukey tests. For the executive/visuoconstruction index, the mild WMA group obtained a better score than both the moderate WMA ($p < 0.001$) and the severe WMA ($p < 0.001$) groups. Also, the moderate WMA group obtained a better score than the severe WMA group ($p < 0.001$) (figure).

On the language/memory index, the mild WMA group displayed greater impairment than both the moderate WMA ($p < 0.001$) and the severe WMA ($p < 0.001$) groups. The moderate and severe WMA groups did not differ on the memory/language index.

Within-group comparisons were carried out with paired *t* tests. Participants in the mild WMA group obtained a

Table 5 *WMA within-group performances on executive/visuoconstructive vs memory/language indexes: z score mean (SD)*

	Executive/ visuoconstruction	Memory/ language	Significance
Mild WMA	−1.42 (0.77)	−4.00 (1.68)	$p < 0.001$
Moderate WMA	−2.66 (1.57)	−1.88 (1.60)	NS
Severe LA	−4.41 (1.48)	−1.41 (0.83)	$p < 0.001$

WMA = white matter abnormality; LA = Leukoaraiosis Scale.

lower score, demonstrating worse performance on language/memory index than the executive/visuoconstruction index ($t[30] = 8.91$, $p < 0.001$). The opposite profile was observed in the severe WMA group. These participants obtained a lower score on the executive/visuoconstruction index than the memory/language index ($t[16] = 7.79$, $p < 0.001$). For the moderate WMA group, there was no within-group difference between the executive/visuoconstruction and memory/language indexes (table 5).

Discussion. Our first finding replicates prior studies that report an association between WMA observed on MRI and poor performance on tests of executive control.[36-39] In our sample of patients with dementia with varying degrees of WMA, we found that an increase in WMA was associated with greater impairment on measures of executive control and visuoconstruction abilities. Higher degrees of WMA, however, were not associated with an incremental impairment in memory and language abilities.

We examined the association between the MMSE[34] and MRI WMAs and found no significant association between WMAs and performance on the MMSE. The failure to find an association between the degree of WMA and the scores on the MMSE is because the MMSE primarily assesses memory and cognitive functions such as language and provides little assessment of executive functions.[40] Thus, the MMSE would be a relatively insensitive instrument in the assessment for the presence and degree of subcortical VaD.

The reasons why WMAs induce deficits of executive functions are not entirely known, but intra- and interhemispheric communications have been reported to be critical for normal cognitive functioning.[41] This communication is often mediated by myelinated axons that travel in the subcortical white matter, and damage to the white matter can induce disconnection syndromes. The frontal lobes are reciprocally connected to more supramodal, polymodal, and unimodal cortical regions than any other lobe. In addition, the frontal lobes have extensive connections with portions of the limbic system, the basal ganglia, and the thalamus. Anatomists have suggested that these extensive connections allow the frontal lobe to control executive functions.[42] Thus, the neurologic mechanisms for the observed relationships between neuropsychological dysfunction and WMA are most likely due to the disruption of these frontal–subcortical white matter connections.

Different anatomic portions of the white matter connect different structures.[43,44] For example, some investigators divide the cerebral white matter into an outer zone that contains the "radiate" compartment and an inner zone that contains sagittal and bridging system compartments. The radiate compartment corresponds primarily to the corona radiata but also contains the U fibers. The sagittal compartment has four sets of fiber systems: the systems that link the thalamus and basal ganglia to the cortex, the long ipsilateral association fiber systems (associative fasciculi), the interhemispheric connections, and the cortical projections to the brainstem and spinal cord. In addition, the white matter in the radiate system can be subdivided by their lobar position. We posit that if specific regions of interest such as the white matter in the frontal lobes or the white matter that links the basal ganglia and frontal lobes were specifically evaluated, executive/visuoconstructive disabilities might account for a greater proportion of the variance as compared with other areas such as the white matter in the occipital lobes or the posterior limb of the internal capsule.

In addition to white matter changes, some of our VaD patients (n = 15) had lacunes involving subcortical gray matter structures (i.e., basal ganglia). As noted above, comparisons betweens VaD patients with and without lacunes yielded no differences on any neuropsychological tests. It is interesting to speculate whether subcortical white disease per se might have a direct and deleterious effect on subcortical gray matter structures such as the basal ganglia. Several investigators have speculated that the inhibitory actions of the basal ganglia serve to selectively gate cortically mediated information processing.[45,46] Thus, when the basal ganglia are damaged or become disinhibited, the frontal lobes may not be able to effectively maintain or shift mental set as required by some tasks. An impairment in this type of gating mechanism might explain the impaired performance of VaD patients on complex mental control and verbal fluency tasks.[17]

In contrast to the strong relationship between executive/visuoconstruction abilities and WMA, performance on memory and language tests did not decline with increasing WMA severity. Rather, less WMA was associated with increased impairment in memory and language abilities. This finding suggests that functional abnormalities induced by WMAs are not producing impairments in memory and language and that some other pathologic factor(s), such as the neuronal degeneration in the medial temporal and the inferior parietal lobes that is associated with AD, might be inducing these memory and language changes.

Another major finding of this study suggests that approximately one-fourth of the hemispheric white matter needs to be involved for executive dysfunction to become manifest.[4] As demonstrated by the severe

WMA group, however, the point at which executive dysfunction exceeds memory impairment occurred only when about 50% of the hemispheric white matter was involved. It is this 50% threshold that typifies the proposed diagnostic criteria for subcortical VaD.[10] As mentioned above, patients who have dementia but demonstrate little to no WMA primarily exhibit memory/language impairments that are the hallmark features of AD. Between these two extremes is the moderate WMA group whose neuropsychological profile demonstrates an equivalent impairment on the executive/visuoconstruction and language/memory indexes. A 50% WMA threshold, therefore, might be too stringent to diagnose subcortical VaD. Thus, the proposed research criteria for subcortical vascular dementia[10] might need to be tempered to include a neurocognitive profile of equal impairment on executive and memory measures. In a more recent article,[47] it was suggested that VaD is now seen to encompass a heterogeneous group of clinical syndromes and that many patients with VaD have coexistent AD. This combination of VaD and AD is frequently termed "mixed dementia," and this combination might represent another important but previously underestimated subgroup. Hence, our cases in the moderate WMA group who had approximately one-fourth of their white matter involved and equal impairment on executive and language/memory tests might be examples of a mixed dementia.

The current study has limitations. First, differential impairment on tests of executive control corroborated by an increase in neurofibrillary tangles in the frontal lobes occurs in AD.[48] Indeed, executive control dysfunction can be an early and initial symptom of AD.[49,50] Thus, it is possible that the differentially worse performance on executive control tests seen in some of our participants could be due to gray matter rather than white matter pathology. An interaction between gray and white matter pathology is also possible. Disambiguating the contribution of type and location of neuropathology as related to AD and VaD is an area that requires additional research. Another limitation is that MRI data were not obtained for the healthy aged-matched control subjects. This would have been helpful in assessing the white matter threshold for dementia. Also, the use of more sophisticated computer-assisted techniques to measure MRI WMAs could have yielded different results. Third, studies using other neuropsychological and imaging protocols would add to the validity of our findings. Despite these limitations, the data described above suggest that conventional MRI techniques and easily administered neuropsychological tests can be combined to characterize the effect of WMAs on neuropsychological functioning in patients with mild dementia.

Acknowledgment

The work of Stefan Skalina, MD, and Jon Bonivita, MD, from the Department of Radiology, Crozer-Chester Medical Center, is gratefully acknowledged.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Press, 1994.
2. Wetterling T, Kanitz RD, Borgis KJ. The ICD-10 criteria for vascular dementia. Dementia 1994;5:185–188.
3. Chui HC, Victoroff JI, Margolin D, et al. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992; 42: 473–480.
4. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–260.
5. Chui HC, Mack W, Jackson JE, et al. Clinical criteria for the diagnosis of vascular dementia: a multicenter study of comparability and interrater reliability. Arch Neurol 2000;57:191–196.
6. Gold G, Bouras C, Canuto A, et al. Clinicopathological validation study of four sets of clinical criteria for vascular dementia. Am J Psychiatry 2002;159:82–87.
7. Gold G, Giannakopoulos P, Montes-Paixao Junior C. et al. Sensitivity and specificity of newly proposed clinical criteria for possible vascular dementia. Neurology 1997;49:690–694.
8. Pohjasvaara T, Mantyla R, Ylikoski R, Kaste M, Erkinjuntti T. Comparison of different clinical criteria (DSM-III, ADDTC, ICD-10, NINDS-AIREN, DSM-IV) for the diagnosis of vascular dementia. National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences. Stroke 2000; 31:2952–2957.
9. Cosentino SA, Jefferson AL, Carey M, et al. The clinical diagnosis of vascular dementia: a comparison between four classification systems and a proposal for a new paradigm. Clin Neuropsychol 2004;18:83–100.
10. Erkinjuntti T, Inzitari D, Pantoni L, et al. Research criteria for subcortical vascular dementia in clinical trials. J Neural Transm [Suppl] 2000;59:23–30.
11. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol 2002;1:426–436.
12. Libon DJ, Bogdanoff B, Cloud BS, et al. Declarative and procedural learning, quantitative measures of the hippocampus, and subcortical white alterations in Alzheimer's disease and ischaemic vascular dementia. J Clin Exp Neuropsychol 1998;20:30–41.
13. Libon DJ, Bogdanoff B, Leopold N, et al. Neuropsychological profiles associated with subcortical white matter alterations and Parkinson's disease: implications for the diagnosis of dementia. Arch Clin Neuropsychol 2001;16:19–32.
14. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34:939–944.
15. Junque C, Pujol J, Vendrell P, et al. Leuko-araiosis on magnetic resonance imaging and speed of mental processing. Arch Neurol 1990;47: 151–156.
16. Ylikoski R, Ylikoski A, Erkinjuntti T, et al. White matter changes in healthy elderly persons correlate with attention and speed of mental processing. Arch Neurol 1993;50:818–824.
17. Lamar M, Price CC, Davis KL, Kaplan E, Libon DJ. Capacity to maintain mental set in dementia. Neuropsychologia 2002;40:435–445.
18. Wechsler D. A standardized memory scale for clinical use. J Psychol 1945;19:87–95.
19. Paulesu E, Frith CD, Frackowiak RS. The neural correlates of the verbal component of working memory. Nature 1993;362:342–345.
20. Goodglass H, Kaplan E. The assessment of aphasia and related disorders. 2nd ed. Philadelphia: Lea & Febiger, 1983.
21. Libon DJ, Malamut BL, Swenson MR, Cloud BS. Further analysis of clock drawings among demented and non-demented subjects. Arch Clin Neuropsychol 1996;11:193–211.
22. Cosentino S, Jefferson A, Chute DL, Kaplan E, Libon DJ. Clock drawing errors in dementia: neuropsychological and neuroanatomical considerations. Behav Cogn Neurol 2004;17:74–84.
23. Libon DJ, Swenson R, Baronski EJ, Sands LP. Clock drawing as an assessment tool for dementia. Arch Clin Neuropsychol 1993;8:405–415.
24. Stern RA, Javarsky DJ, Singer EA et al. The Boston Qualitative Scoring System for the Rey–Osterrieth Complex Figure. Odessa, FL: Psychological Assessment Resources, Inc., 1999.
25. Freeman RQ, Giovannetti T, Lamar M, et al. Visuoconstructional deficits in dementia. Neuropsychology 2000;14:415–426.
26. Carew TG, Lamar M, Cloud BS, Grossman M, Libon DJ. Impairment in category fluency in ischemic vascular dementia. Neuropsychology 1997; 11:400–412.
27. Gourovitch ML, Kirkby BS, Goldberg TE, et al. A comparison of rCBF patterns during letter and semantic fluency. Neuropsychology 2000;14: 353–360.
28. Mummery CJ, Patterson K, Hodges JR, Wise RJ. Generating "tiger" as an animal name or a word beginning with T: different brain activation. Proc R Soc Lond B 1996;263:989–995.

29. Libon DJ, Mattson RE, Glosser G, et al. A nine-word dementia version of the California Verbal Learning Test. Clin Neuropsychol 1996;10:237–244.
30. Goldberg E, Barr W. Selective knowledge loss in activational and representational amnesias. In: Squire LR, Butters N, eds. The neuropsychology of memory. New York: Guilford Press, 1992.
31. Davis KL, Price CC, Kaplan E, Libon DJ. Error analysis of the nine-word California Verbal Learning Test (CVLT-9) among older adults with and without dementia. Clin Neuropsychol 2002;16:81–89.
32. Yuspeh RL, Vanderploeg RD, Crowell TA, Mullan M. Differences in executive functioning between Alzheimer's disease and subcortical ischemic vascular dementia. J Clin Exp Neuropsychol 2002;24:745–754.
33. Salmon DP. Cognitive abilities mediated by frontal-subcortical circuits. In: Lichter DG, ed. Frontal-subcortical circuits in psychiatric and neurological disorders. New York: Guilford Press, 2001: 114–150.
34. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
35. Yesavage J. The use of self-rating depression scales in the elderly. In: Poon LW, ed. Handbook of clinical memory assessment of older adults. Washington, DC: American Psychological Association, 1986: 213–217.
36. O'Brien, JT, Wiseman R, Burton EJ, et al. Cognitive associations of subcortical white matter lesions in older people. Ann NY Acad Sci 2002;977:436–444.
37. Roman GC, Royall DR. Executive control function: a rational basis for the diagnosis of vascular dementia. Alzheimer Dis 1999;13(suppl 3): S69–S80.
38. Starkstein SE, Sabe L, Vazquez S, et al. Neuropsychological, psychiatric, and cerebral blood flow findings in vascular dementia and Alzheimer's disease. Stroke 1996;27:408–414.
39. Vanderploeg RD, Yuspeh RL, Schinka JA. Differential episodic and semantic memory performance in Alzheimer's disease and vascular dementia. J Int Neuropsychol Soc 2001;7:563–573.
40. Jefferson AL, Cosentino SA, Ball SK, et al. Errors produced on the Mini-Mental State Examination and neuropsychological test performance in Alzheimer's disease, ischemic vascular dementia, and Parkinson's disease. J Neuropsychiatry Clin Neurosci 2002;14:311–320.
41. Geschwind N. Disconnexion syndromes in animals and man. Brain 1965;88:237–294.
42. Nauta WJH. The problem of the frontal lobe: a reinterpretation. J Psychiatr Res 1971;8:167–187.
43. Behrens TE, Johansen-Berg H, Woolrich MW, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat Neurosci 2003;6:750–757.
44. Mesulam MM. Large-score networds, association cortex, frontal systems, the limbic system, and hemispheric specializations. In: Mesulam MM, ed. Principles of behavioral and cognitive neurology. 2nd ed. New York: Oxford University Press, 2000: 1–120.
45. Beiser DG, Houk JC. Model of cortical-basal ganglionic processing: encoding the serial order of sensory events. J Neurophysiol 1998;79:3168–3188.
46. Frank JM, Loughtery B, O'Reilly, R. Interactions between frontal cortex and basal ganglia in working memory: a computational model. Cogn Affect Behav Neurosci 2001;1:137–160.
47. Erkinjuntti T. Clinical deficits of Alzheimer's disease with cerebrovascular disease and probable VaD. Int J Clin Pract [Suppl] 2001;120:14–23.
48. Johnson JK, Head E, Kim R, Starr A, Cotman CW. Clinical and pathological evidence for a frontal variant of Alzheimer disease. Arch Neurol 1999;56:1233–1239.
49. Sgaramella TM, Borgo F, Mondini S, et al. Executive deficits appearing in the initial stage of Alzheimer's disease. Brain Cogn 2001;46:264–268.
50. Binetti G, Magni E, Padovani A, Cappa SF, Bianchetti A, Trabucchi M. Executive dysfunction in early Alzheimer's disease. J Neurol Neurosurg Psychiatry 1996;60:91–93.